REMARKS

Claims 1-13 remain pending in the present application. The amendment to claim 13 merely corrects a typographical error. No new matter is entered.

Rejection under 35 U.S.C. 103 over Adachi et al. in view of Sheffield et al.

Claims 1-13 are rejected under 35 U.S.C. §103(a) as obvious over Adachi et al. in view of Sheffield et al. Applicants traverse this basis for rejection and respectfully request reconsideration and withdrawal thereof, in view of the accompanying amendment.

At page 3 of the outstanding Office Action, the Examiner states:

> Adachi describes how to prevent postoperative intraperitoneal adhesions by oral administration of composition comprising tranilast and carboxymethylcellulose prior to and after surgery (see the whole document with emphasis on the abstract and page 52). The carboxymethylcellulose meets the limitation of delivery vehicle of claim 1. Therapeutically effective amount as recited in claim 1 is any amount deemed effective by the artisan. Administration of 60 mg/kg per day represents a single dose as recited in claim 8 and also meets the limitation of claim 11. The carboxymethyl cellulose is a sustained release excipient so that the composition administered is in sustained release form meeting claims 9 and 10. The oral administration of tranilast composition prior to surgery meets the limitations of systemic administration and thus meets claims 12 and 13. The melted tranilast and the carboxymethylcellulose are in solution so that the carrier composition in claim 3 is met.
>
> Adachi does not teach that the composition comprising tranilast is locally administered to tissue at surgical sites to treat adhesions. But, local and/or topical administration of therapeutic agents at

> surgical sites to treat or inhibit adhesion formation is known for various agents. (Emphasis added).

The Examiner recognizes that Adachi et al. fail to disclose or suggest local administration of Tranilast directly onto tissue surfaces at sites subject to adhesion formation, and attempts to cure the deficiencies of Adachi et al. by citation of Sheffield et al., which discloses local administration of NSAID compounds to treat adhesions.

> Sheffield discloses method of inhibiting the formation of post surgical adhesion by administration of compositions to the site of surgical trauma to inhibit the post surgical adhesion (abstract; column 2, lines 34-38; column 3, lines 15-28,39-56). The composition locally or topically administered at the surgical site comprises non-steroidal anti-inflammatory drug (NSAID) and pharmaceutically acceptable carrier (column 4, lines 12-29); when the composition is carried in a liposome or when the NSAID is encapsulated in a microcapsule, the composition of Sheffield meets the requirements of claim 3; when the polymeric carrier is lactide, the composition of Sheffield meets the requirements of claim 4. Furthermore, Sheffield teaches that the composition can be applied by catheterization using implanted osmotic pump (column 3, lines 29-38) so that when the delivery method is by osmotic pump, the requirement of claim 3 is met. (Office Action, page 4; emphasis added).

The Examiner concludes that it would have been obvious to the skilled artisan to combine the teachings of the cited references to reach the presently claimed inventive method.

> Therefore, taking the teachings of Adachi and Sheffield, one having ordinary skill in the art at the time the invention was made would have reasonably expectation of success that topical or oral administration anti-adhesion composition of Adachi or Sheffield or the combined composition of Adachi and Sheffield would produce the expected inhibition of post surgical adhesion. (Office Action, pages 4-5; emphasis added).

References are Improperly Combined

As discussed in Applicants' response of February 25, 2010, Sheffield et al. is directed strictly to topical administration of NSAIDS for adhesion prevention. NDSAIDS are a completely different class of pharmaceuticals as compared to Tranilast, with completely different biological activities as compared to Tranilast. As such, one skilled in the art would not consider Tranilast a substitute for NSAIDS, whether administered orally or topically. As such, the Examiner's proposed combination lacks scientific support. There is no reason the skilled artisan would look to a reference directed to NSAIDS and draw any conclusion regarding Tranilast.

> '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR International Co. v. Teleflex Inc.*, 550 U.S. at ___, 82 USPQ2d at 1396.

The only apparent reason that the Examiner combines the references is that they separately teach the present claim limitations, and are both directed to (quite different) ways of reducing adhesions. However, no logical or scientific reasoning supports the proposed combination.

Withdrawal of the rejection is requested on this basis alone, since the references are improperly combined, and therefore cannot establish a prima *facie case* of obviousness as to the present claims.

Success of Combination is Unpredictable

Further, the Examiner's proposal that because a particular pharmaceutical (in this case Tranilast) is known to have a particular efficacy through oral administration, that it would necessarily have similar efficacy if administered

topically is scientifically questionable at best and certainly in the realm of the unpredictable. The U.S. Supreme Court in *KSR* relied heavily on the predictability of prior art combinations in assessing the validity of obviousness rejections:

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at ___, 82 USPQ2d at 1396. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. **MPEP 2143 (A)** (Emphasis added).
>
> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007). **MPEP 2143.01 (III).** (Emphasis added).

As the Examiner is well-aware, oral administration routes the pharmaceutical through the alimentary system, wherein it is acted upon by multiple body chemistries, which often result in modification of the original pharmaceutical compound into various derivatives and/or reaction products (metabolites), which are the efficacious compounds. If administered topically, there is no guarantee, or even a reasonable expectation that similar chemistries will occur, and therefore topical efficacy cannot be predicted, or even reasonably expected.

In response to Applicants' arguments as to the unpredictability of the use of topical administration of compounds known useful for oral administration, the Examiner stated:

> Applicant argues that topical efficacy cannot be predicted or even reasonably expected for tranilast. The examiner disagrees because it is known to inhibit post surgical adhesions by topical administration to surgical sites, it is also known that tranilast inhibits post surgical adhesions, thus, it would be reasonable to expect that tranilast can be administered by any of the known method to inhibit post surgical adhesions except [where] there is reason to bar the topical administration of the tranilast. So far, applicant has not provided such a reason. (Advisory Action of March 26, 2010, page 3; emphasis added).

Applicants respectfully submit that the Examiner's argument is circular, and fails to address the issues raised in their response of February 25, 2010, repeated above, which provides the "reason" that the skilled artisan would have had no expectation of success in topically administering Tranilast to potential adhesion sites following surgery, i.e. efficacy of oral administration of a drug cannot predict its efficacy upon topical administration due to the entirely different body chemistries involved in the vastly different administration routes. The Examiner's argument, quoted above, seems to suggest that any drug which is known for use in oral administration would have similar effects if administered topically. If this is the Examiner's position, Applicants request that the Examiner provide published evidence to this effect.

In the absence of such written evidence from the Examiner, Applicants submit that, on a scientific basis, the skilled artisan could not predict success in inhibiting intraperitoneal adhesions via topical administration of Tranilast to surgical sites, and as such no *prima facie* case of obviousness has been established in the combination of Adachi and Sheffield et al.

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007). **MPEP 2143.01 (III).** (Emphasis added).

Withdrawal of the rejection is requested on this basis alone.

Adachi is Non-Enabling Prior Art

The data in the present specification demonstrates that orally administered Tranilast is ineffective against adhesions, contrary to the study disclosed in Adachi. For this reason, Applicants submit that Adachi is non-enabling prior art, and therefore ineffective as a reference. Some case law regarding the use of non-enabling references as prior art is cited below.

> While a reference must enable someone to practice the invention in order to anticipate under § 102(b), a non-enabling reference may qualify as prior art for the purpose of determining obviousness under § 103. *Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 652, 223 U.S.P.Q. (BNA) 1168, 1173 (Fed. Cir. 1984) (reference that lacks enabling disclosure is not anticipating, but "itself may qualify as a prior art *reference* under § 103, but only for what is disclosed in it" (emphasis in original)); see *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 U.S.P.Q.2d (BNA) 1301, 1304 (Fed. Cir. 1989) ("even if a reference discloses an inoperative device, it is prior art for all that it teaches"). *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991). (Underlining added).

As the Examiner indicates, Adachi discloses oral administration of Tranilast for inhibition of adhesion formation, but is silent regarding topical administration to surgery sites. Applicants have discussed the Adachi (i.e. "Shinya") reference and its shortcomings in the present application.

> The compound N-(3,4-dimethoxycinnamoyl) anthranilic acid, commonly known as Tranilast, also has been examined as an adhesion prevention agent in rats, (Shinya, A., et. al. (1999), "The Prevention of Postoperative Intraperitoneal Adhesions by Tranilast: N-(3,4-dimethoxycinnamoyl) Anthranilic Acid," Jpn J. Surg. 29:51-54). In this study, Shinya, et al. used oral, systemic dosing both pre- and post-operatively in a rat intraperitoneal adhesion model. Of significant note, however, ischemia via abrasion of the surgical site was not performed in the model utilized in this study. Therefore, it is believed that the type of trauma necessary to cause loss of blood flow and to more accurately mimic the clinical situation in humans was not present. It is such a loss of blood flow that strongly contributes to reduced tissue plasminogen activity, fibrin deposition and adhesion formation. Accordingly, it is believed that the value and validity of such a study with respect to the efficacy of systematic administration of Tranilast for inhibition or prevention of adhesions is questionable. (Specification, page 5, lines 6-26; emphasis added).

In conducting their study, Adachi/Shinya et al. discuss the intraperitoneal adhesion model used therein:

> Initially, we established an intraperitoneal adhesion model in rats based on Ryan et al.'s experiments,... (Page 51, right column, top; emphasis added).
>
> The small intestine approximately 15 cm proximal to the cecum was incised about halfway round and closed with continuous sutures using 5-0 polyglactin in a single layer, followed by drying for 5 min. Next, 1.0 ml blood was sprinkled on the dried area. The abdominal wall was closed with 3-0 silk interrupted sutures. (Page 51, right column, bottom).

The Ryan et al. reference is footnoted as #5, which upon review of the footnotes indicates that the study was published in 1971, eighteen years prior to publication of Adachi/Shinya's study. Notably, Adachi fails to disclose or suggest abrasion of the organs at the surgical site whatsoever. In the ensuing years, many references disclose utilizing the abrasion test for evaluating adhesions, and Applicants submit that this preparation technique, also used in the present evaluations, is in fact the art-accepted preparation for adhesion evaluation.

> It is well known that undesired tissue damage results from most surgical procedures, where cutting, desiccation, ischemic, and manipulative abrasions occur. Suture lines at closed incisions, as well as areas of abrasive contacts that occur between tissue surfaces and the many devices used in surgery (i.e., clamps, gloves, sponges, etc.) are known to be problematic, and often painful sites, which result from damaged cell membrane surfaces...(U.S. Patent No. 6,541,460; col. 2, lines 34-49; emphasis added).
>
> The cecum was elevated and isolated by moist gauze. The proximal end of the cecum was emptied of its contents. A 1 cm×2 cm area on the anterior surface of the proximal end of the cecum was gently abraded by rubbing 10 times with dry gauze. The cecum was then scraped with a scalpel blade to cause minute petechial hemorrhages. The cecal abrasion was left exposed for 15 minutes. After 15 minutes, the cecal abrasion and the abdominal wound were blotted with a gauze sponge to gently remove any excess blood and ensure complete hemostasis. Placement of these two wounds together normally leads to reproducible formation of an adhesion. (U.S. Patent No. 5,795,584; col. 14, lines 22-34; emphasis added).
>
> This example illustrates the high incidence of peritoneal adhesions observed using a rat abdominal surgery model involving normal laparotomy with controlled cecal abrasion to afford an example of severe tissue trauma in such surgery and to be a control for comparison with the adhesions preventive materials and method of use of this invention. (U.S. Patent No. 6,086,907; col. 6, lines 34-40; emphasis added).

Even the cited reference to Sheffield et al., issued nine years prior to Adachi, uses this more rigorous preparation technique for evaluation testing.

> New Zealand white female rabbits (1.8-2.0 kg) underwent midline laparotomy using acelepromazine and ketamine anesthesia. A 3x5 cm abrasion was produced over the right-lateral peritoneal side-wall by scraping the surface peritoneum with a scalpel until punctate bleeding developed over the entire 3x5 cm area. (U.S. Patent No. 4,937,254; col. 7, lines 35-40; emphasis added).

Accordingly, as indicated in the present specification (quoted above), Applicants submit that the testing regime set forth in Adachi was at least outmoded at the time of its publication, if not entirely meaningless.

In the present specification, Applicants disclose use of this more rigorous model for adhesion evaluation in their testing.

> In the peritoneal sidewall model, rabbits were pre-anesthetized with 1.2 mg/kg acetylpromazine and anesthetized with a mixture of 55 mg/kg ketamine hydrochloride and 5 mg/kg xylazine intramuscularly. Following preparation for sterile surgery, a midline laparotomy was performed. A 3 cmx5 cm area of peritoneum and transversus abdominis muscle was removed on the right lateral abdominal wall. The cecum was exteriorized and digital pressure was exerted to create subserosal hemorrhages (trauma and loss of blood flow) over all cecal surfaces. The cecum was then returned to its normal anatomic position. (Specification, page 25, lines 3-14; emphasis added).

As set forth in Applicants' previous response, the data in Tables 14 and 15, directed to oral administration of Tranilast was ineffective in reducing formation of adhesions, contrary to the teaching of Adachi/Shinya. Aside from the above-discussed preparation technique, the testing regime was identical to that of Adachi/Shinya.

> Tranilast in the melted form mixed in 0.5% carboxymethyl cellulose sodium (CMC) was given orally to ten rats at a dose of 60 mg/kg per day for 5 days prior to the operation, then from the second postoperative day, 60 mg/kg per day was given orally until the end of the study. All of the rats were killed 3 weeks after the operation. (Adachi, page 52, left column, top).

> According to the present specification:

> Groups of animals received either oral dosing, or local delivery of Tranilast, or placebo control. In the animals that received local delivery, a single pump, filled with placebo (70% Polyethylene

glycol 400, 20% Tween 80, 10% N,N-dimethylacetamide (DMAC)), or Tranilast (6.25 mg/ml), at 10 microliter/hour over 7 days starting with the day of surgery, was placed in the subcutaneous space. Certain animals received oral dosing (approximately 60 mg/kg). Oral dosing was either pre-operatively (once a day for the 5 days prior to surgery, with the last dose given 2 hours prior to surgery) or, in one group, pre- and post-operatively (from day 2 through day 21 post-surgery). For further clarification, the treatment groups are shown below. (Specification, page 33, line 7, bridging to page 34; emphasis added).

Thus, contrary to the Examiner's representations in the Advisory Action of March 26, 2010, the testing to establish the efficacy of Adachi's oral dosing regime was identically conducted in the present application; as to dosage (60 mg/kg), pre-operative dosing (5 days) and post-operative dosing (21 days/3 weeks). As set forth in Applicants' response of February 26, 2010, Tables 12 (placebo) and 14 are indicative of the failure of oral administration of Tranilast.

TABLE 12

Adhesion Scores in Placebo Treated Animals

Animal Number	Adhesion Area Percentage	Adhesion Tenacity
1	100	2
2	100	3
3	100	3
4	100	3
5	100	2
6	100	3
7	100	3

TABLE 14

Adhesion Scores in Animals Treated with 60 mg/kg Tranilast (5 Days Pre-operatively and 21 days Post-operatively)

Animal Number	Adhesion Area Percentage	Adhesion Tenacity
1	100	2
2	100	2
3	100	2
4	100	2
5	100	2
6	Died	
7	100	2

(Copied from US 2005/0106229 A1).

As is clear from the Table 14 data, the "Adhesion Area Percentage" for each orally dosed animal was 100%, no different than the placebo group (Table 12). Thus, contrary to the teachings of Adachi/Shinya, oral administration of Tranilast does not "reduce the area percentage of adhesions formed" (claim 1), as compared to no treatment at all. Clearly, Adachi/Shinya has been demonstrated to be non-enabling by the testing data set forth above. Oral administration of Tranilast does not work.

Further, since the use of non-enabling prior art is limited "under § 103, ...only for what is disclosed in it", *Beckman Instruments, Inc. v. LKB Produkter AB* (cited above), one skilled in the art could certainly not have drawn any predictable conclusions from Adachi as to the efficacy of Tranilast against intraperitoneal adhesions when delivered by an undisclosed administration route (i.e. topical administration at the surgery site).

As such, Applicants respectfully submit that Adachi/Shinya is ineffective as a reference, and therefore cannot be combined with any other reference,

since Adachi has been demonstrated to lack predictability (*KSR*) in the effect of Tranilast, even as to oral administration.

Withdrawal of the rejection for failure to establish a *prima facie* case of obviousness is requested.

In view of the foregoing, it is respectfully submitted that the present claims are in condition for allowance. Prompt notification of allowance is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 50-2478 (14924).

If the Examiner has any questions or wishes to discuss this application, the Examiner is invited to contact the undersigned representative at the number set forth below.

Respectfully submitted,

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